Movement disorders in inborn errors of metabolism

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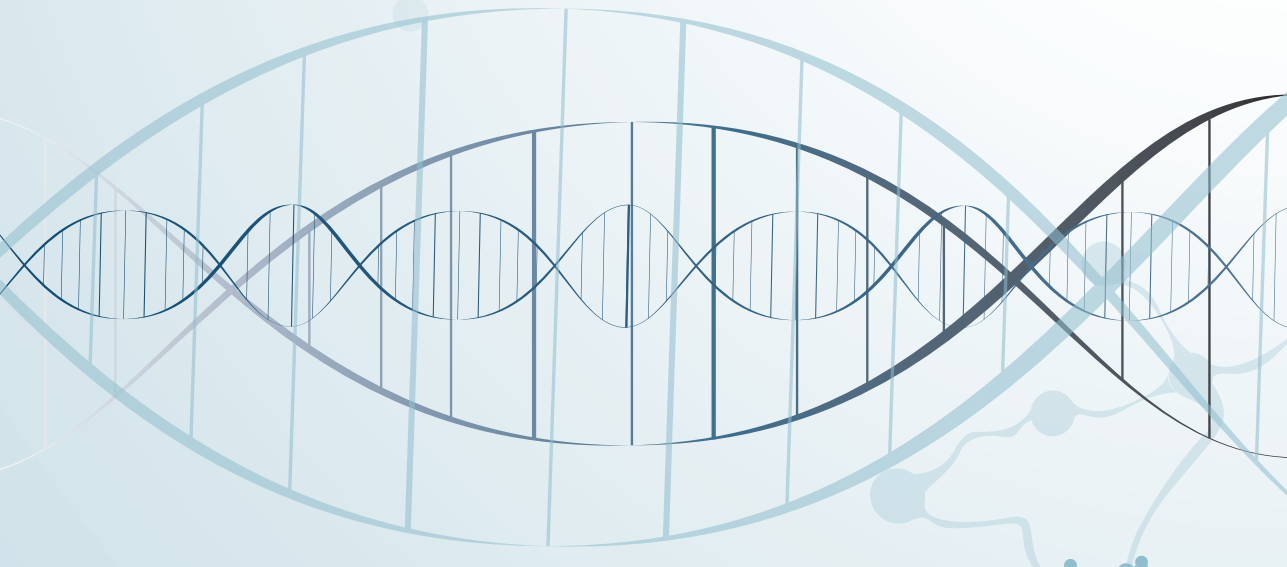
Chapter 2



Dystonia in children and adolescents: a systematic review and a new diagnostic algorithm

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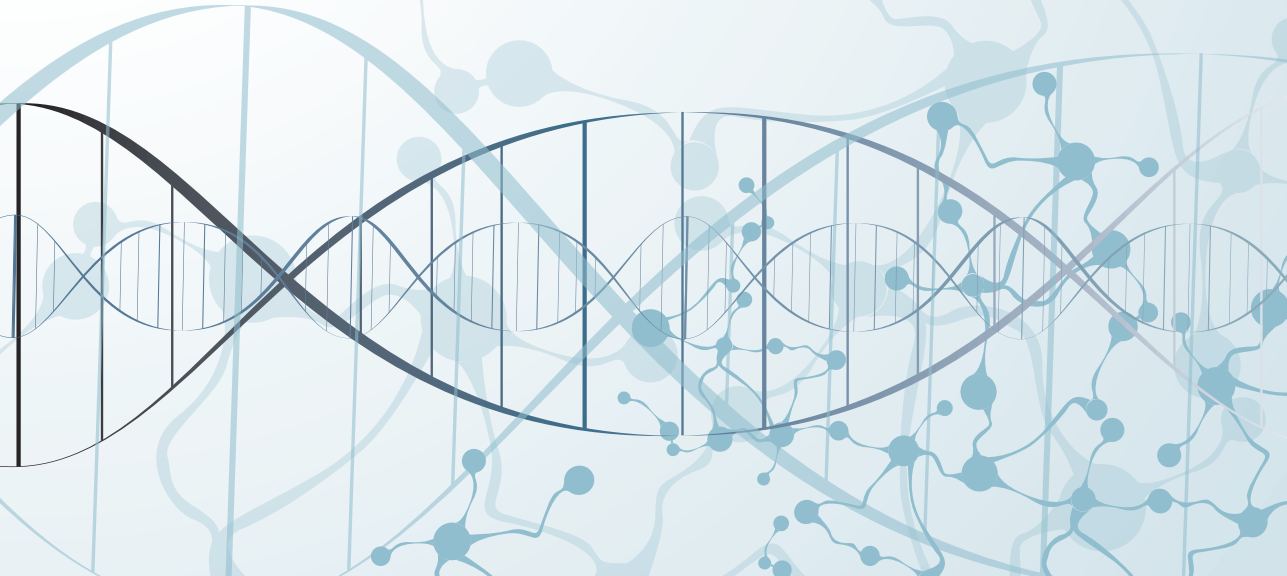


Abstract

Early etiological diagnosis is of paramount importance for childhood dystonia because some of the possible underlying conditions are treatable. Numerous genetic and non-genetic causes have been reported, and diagnostic workup is often challenging, time consuming and costly. Recently, a paradigm shift has occurred in molecular genetic diagnostics, with next-generation sequencing techniques now allowing us to analyse hundreds of genes simultaneously. To ensure that patients benefit from these new techniques, adaptation of current diagnostic strategies is needed. On the basis of a systematic literature review of dystonia with onset in childhood or adolescence, we propose a novel diagnostic strategy with the aim of helping clinicians determine which patients may benefit by applying these new genetic techniques and which patients first require other investigations. We also provide an up-to-date list of candidate genes for a dystonia gene panel, based on a detailed literature search up to 20 October 2014. While new genetic techniques are certainly not a panacea, possible advantages of our proposed strategy include earlier diagnosis and avoidance of unnecessary investigations. It will therefore shorten the time of uncertainty for patients and their families awaiting a definite diagnosis.

2.1 – Introduction

Dystonia is a movement disorder characterised by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.[1] For dystonia in children and adolescents, here referred to as dystonia of childhood (DC), the list of possible genetic and non-genetic causes is extensive.[2,3] For clinicians encountering a young patient with dystonia, an important practical question is how to manage the diagnostic work-up, which is often challenging, time-consuming and costly.

Recently, a paradigm shift has occurred in molecular genetic diagnostics, with next-generation sequencing (NGS) techniques now allowing us to analyse hundreds of genes simultaneously. NGS diagnostic strategies are particularly effective in heterogeneous conditions, including movement disorders, significantly increasing the diagnostic yield at lower costs.[4,5] As a significant proportion of DC cases is estimated to be genetic, a 'genetics first' diagnostic approach for all patients with DC seems logical and appealing. However, there are two groups of patients for whom another initial approach should be considered. First, in children and adolescents who may have acquired dystonia, and second, in patients in whom the cause may be a treatable inborn error of metabolism (IEM), because for most of these IEM biochemical investigations will be a faster diagnostic method than genetic testing.

We first provide a systematic literature review of the phenomenology, classification, and etiology of DC. We then propose a novel diagnostic strategy that will help clinicians determine which patients may benefit from NGS technologies and which patients require other initial investigations. Finally, we give an up-to-date list of dystonia gene candidates to enhance the development of NGS diagnostics for DC (supplementary **Table S1**).

2.2 – Methods

We systematically reviewed all papers regarding DC up to October 20th 2014, both genetic and non-genetic, in three age groups (infancy, childhood and adolescence), as proposed in the latest dystonia classification.[1] For details of our systematic search, see supplementary **Box S2**.

2.3 – Dystonia in children and adolescents: state of the art

2.3.1 – Phenomenology: Is it dystonia?

The first step in diagnosing DC is the identification of a hyperkinetic movement as being 'dystonic'. Dystonia is defined as "*a movement disorder characterised by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both. Dystonic movements are typically patterned or twisting, and may be tremulous. They are often initiated or*

worsened by voluntary action and associated with overflow muscle activation."[1] This definition of dystonia is identical for adults and children[1,3] and similar to the definition of dystonia published by the Taskforce on Childhood Movement Disorders.[6] In children, dystonia is more often generalised compared with adult-onset dystonia.

Correct identification of dystonia involves both an understanding of classification systems and visual pattern recognition. Three important, characteristic, clinical features of dystonia are: (1) patterned, predictable contractions of the same muscles; (2) exacerbation when performing voluntary movements (e.g. walking, running, writing) and (3) the so-called *geste antagoniste*, or sensory trick. This phenomenon is characterised by the relief of dystonic movements by lightly touching the relevant or adjacent part of the body. A sensory trick is particularly frequent in cranial and cervical dystonia, whereas limb and trunk involvement more often predominate in children. Therefore, a sensory trick is not an obligatory feature in DC; however, when observed, it strongly favours a diagnosis of dystonia.[1,6]

In children, movements should be evaluated in relation to their developmental age. For instance, a healthy toddler can have normal overflow movements that may look like dystonia, diminishing as the child's development progresses.[3] In addition to these normal movements, abnormal movements may also mimic dystonia (**Table 1**). For example, children with focal, stereotyped movements of the eyelids, face, or neck, are more likely to have tics than focal dystonia.[7,8]

Reliable diagnostic criteria for different body localisations of dystonia are needed to help clinicians accurately differentiate dystonia from conditions mimicking dystonia. Recently a diagnostic guideline for diagnosing blepharospasm has been validated;[9] however, blepharospasm is a form of focal dystonia that rarely occurs in childhood or adolescence. For other body localisations of dystonia specific diagnostic criteria are an unmet need.

2.3.2 – Classification of dystonia

The most recent general classification scheme of dystonia identifies two distinct axes: axis I - clinical characteristics, and axis II – etiology.[1] Axis I describes the clinical features by (1) age at onset, (2) body distribution, (3) temporal pattern, (4) coexistence of other movement disorders and (5) other neurological or systemic manifestations. Axis II addresses the etiology via two components: (1) nervous system pathology and (2) whether the dystonia is inherited or acquired. Classification of etiology into the categories 'inherited' or 'acquired' differs from traditional classification schemes in which dystonia was classified into primary genetic dystonia or secondary dystonia.[1] The reason for this change was that primary dystonias, heredodegenerative dystonias and dystonia-plus syndromes are all in fact genetic disorders.[1] These three categories are now considered together as 'inherited'. In this review, we elaborate on this recent change in etiologic classification.

Table 1 – Mimics of dystonia in children and adolescents

Type of dystonia	Mimics
Mimics of facial dystonia	Tics Stereotypies Functional
Mimics of cervical dystonia (head tilt)	Tics Stereotypies Trochlear nerve palsy Vestibulopathy Spasmus nutans Acquired nystagmus Congenital muscular torticollis Sternocleidomastoid injuries Benign paroxysmal torticollis of infancy Posterior fossa tumors Tumors in the pineal region Chiari malformation Atlanto axial subluxation (e.g. syndrome of Grisel) Cervical tumors (in cervical cord, bone or soft tissue) Upper spinal cord syringomyelia Juvenile rheumatoid arthritis Sandifer syndrome Klippel-Feil syndrome Functional
Mimics of trunk dystonia	Scoliosis Stiff person syndrome Functional
Mimics of limb dystonia (posturing)	Overflow movements in toddlers (normal developmental movements) Stereotypies Shoulder subluxation Dystonic (tonic) tics Myotonia Neuromyotonia Cramp Satayoshi syndrome Rigidity Spasticity Focal tonic seizures Spasms (hypocalcemia, hypomagnesemia, alkalosis) Deafferentation (pseudoathetosis) Functional
Mimics of generalised dystonia	Self-stimulation Opisthotonus Stiff person syndrome Functional

2.3.3 – Etiology of dystonia

There are many possible etiologies of DC. For this review, we highlight acquired dystonias and treatable IEM because an initial approach other than NGS testing needs to be considered for these conditions. All other genetic causes can be tested at the same time by means of NGS diagnostics.

2.3.3.1 – Acquired dystonias

We focus on acquired forms of dystonia that are relatively common and/or treatable. Drugs and toxic agents that may cause DC are listed in **Table 2**. For other causes of acquired DC, clinical clues and recommended investigations are summarised in **Table 3**.

Table 2 – Drugs and toxic agents that may cause dystonia in children and adolescents

Drugs	
Dopamine receptor blocking drugs	(neuroleptics, antiemetics)
Dopamine depleting drugs	(e.g. tetrabenazine)
Dopamine receptor stimulants	(L-dopa, dopamine receptor agonists)
Antihistaminic drugs	
Tricyclic antidepressants	
Serotonin reuptake inhibitors	
Cholinergic agonists	(e.g. trihexyphenidyl)
Antiepileptic drugs	(especially phenytoin and carbamazepine)
Antimalarials	(e.g. chloroquine, amodiaquine)
Calcium channel blockers	
Disulfiram	
Lithium	
Cocaine	
Toxins	**Main source**
Carbon monoxide	Smoke inhalation, poorly functioning heating systems or fuel-burning devices
Cyanide	Inhalation of smoke, ingestion of toxic household and workplace substances or cyanogenic foods
Manganese	Drinking water with a high concentration of manganese, long-term parenteral nutrition
Methanol	Ingestion of certain industrial products such as antifreeze solution or cleaners
Organophosphate	Exposure to or ingestion of insecticides

Table 3 – Clinical clues suggesting acquired dystonia

Clinical clue	Differential diagnosis	Recommended initial investigations
Acute onset dystonia or rapidly progressive course	– Structural lesion	– Neuroimaging
	– External insult[a]	– Neuroimaging
	– Autoantibody-associated movement disorder	– Autoantibodies in serum and CSF
	– ADEM	– Neuroimaging, CSF
	– Infection	– Neuroimaging, serum, CSF
Unilateral dystonia[b]	– Structural lesion	– Neuroimaging
	– External insult[a]	– Neuroimaging
	– Autoantibody-associated movement disorder	– Autoantibodies in serum and CSF
	– Demyelinating disease[c]	– Neuroimaging, CSF
	– Antiphospholipid syndrome[d]	– Serum investigations
	– CP	– Neuroimaging
Psychiatric symptoms (de novo)	– Autoantibody-associated movement disorder	– Autoantibodies in serum and CSF
	– Infection	– Neuroimaging, serum, CSF
Seizures (de novo)	– Structural lesion	– Neuroimaging
	– Autoantibody-associated movement disorder	– Autoantibodies in serum and CSF
	– Rasmussen's syndrome[e]	– Neuroimaging
	– Infection	– Neuroimaging, serum, CSF
Signs of meningo-encephalitis or encephalitis	– Autoantibody-associated movement disorder	– Autoantibodies in serum and CSF
	– Infection	– Neuroimaging, serum, CSF
Abnormal birth or perinatal history	– CP	– Neuroimaging
Local signs of autonomic disturbances and pain	– CRPS I	– Clinical diagnosis[f]

[a] External insults include head trauma and hypoxic insults caused by near-drowning, cardiac arrest or status epilepticus.
[b] Unilateral dystonia comprises either focal or hemidystonia.
[c] Demyelinating diseases including ADEM, multiple sclerosis and neuromyelitis optica.
[d] Antiphospholid syndrome with or without associated rheumatic disease such as systemic lupus erythematosus should be considered in all children with hemidystonia of unknown origin.
[e] In Rasmussen's syndrome dystonia can be an accompanying sign or the presenting feature.
[f] Criteria for CRPS are described by Mersky et al, see Supplemental references (Supplement 4).
Abbreviations: ADEM: acute disseminated encephalomyelitis; CP: cerebral palsy; CRPS I: complex regional pain syndrome type I.

Drugs and toxic agents

DC can be induced by certain drugs and toxic agents, most commonly neuroleptics and antiemetics (**Table 2**).[7,8] Drug-induced dystonias are categorised into acute dystonic reactions and tardive (chronic use) dystonia. The latter is a well-recognised disorder in adults, but may also occur in children.[7] Acute forms of dystonia may arise after taking a few doses or even after one

administration or accidental ingestion.[8] The dystonia usually disappears rapidly on withdrawing the offending drug.

Cerebral palsy

Dyskinetic cerebral palsy (CP) is the most common cause of acquired DC.[10] CP is a clinical diagnosis, encompassing a group of permanent disorders that cause impairment of movement and posture, attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.[11] Dyskinetic CP is characterised by the presence of choreoathetosis and dystonia[11] and possible etiologies are heterogeneous.[8,12] It is most common in children, born at term, who have experienced adverse perinatal effects, since the basal ganglia are particularly vulnerable to pathogenic events toward the end of gestation.[12] There are guidelines to help identify whether an acute intrapartum event was the likely cause of any particular case of CP.[13] Due to the aggressive treatment of perinatal hyperbilirubinemia, it is now rare to see kernicterus as a cause of dyskinetic CP.[12]

In dyskinetic CP, the hyperkinetic movements are usually bilateral and mostly begin after the first year of life, and progress slowly for several years.[7,8] In children with severe CP, dystonia may be so profound and sustained that it manifests as hypertonia rather than abnormal involuntary movements.[3] Brain MRI demonstrates abnormal findings in about 80% of individuals with CP.[14] Genetic analysis is recommended in those cases where no specific cause can be determined, as several monogenic disorders can present with clinical features similar to CP.[15]

Acquired structural lesions

Structural lesions, such as stroke, neoplasms or structurally abnormal vessels including arteriovenous malformations, may result in unilateral DC (focal or hemidystonia).[7,8] Childhood stroke may result in dystonia if the caudate, lenticular nucleus or thalamus are involved.[7,8] In most cases, the dystonia develops months or even years after the incident.

Autoantibody-associated and autoimmune disorders

Several autoantibody-associated and autoimmune disorders can lead to DC (**Table 3**).[16] We put emphasis on two autoantibody-associated disorders, as early recognition and timely therapy can improve the outcome significantly in these conditions.[16]

Anti-N-Methyl-D-Aspartate Receptor (NMDAR) encephalitis in children is characterised by a combination of seizures, movement disorders, psychiatric symptoms and encephalopathy.[16] The first symptom is often non-psychiatric.[17] In addition to dystonia, multiple movement disorders can be seen in the same patient,[16] the most characteristic being orofacial dyskinesias.[17] Young children often present with temper tantrums, hyperactivity or irritability, whereas in older patients anxiety, psychosis and altered personality are the main psychiatric features observed.[17] Recognition of the combination of symptoms should prompt testing for anti-NMDARs antibodies, both in serum and cerebrospinal fluid (CSF).[17] Brain MRI, EEG and CSF may all show non-specific

abnormalities.[17,18] An underlying neoplasm is found in approximately 6% of girls younger than 12 years but rarely in boys, whereas the association with an ovarian teratoma increases in adolescent girls.[18] Treatment consists of immunotherapy and oncological treatment in those patients with a clinically detectable tumor.[18] Outcome is good in the majority of patients treated early enough.[18]

Autoimmune basal ganglia encephalitis is a syndrome characterised by extrapyramidal movement disorders including dystonia and parkinsonism, sleep disturbance, dysautonomia and psychiatric symptoms.[16] Approximately 70% of cases have serum antidopamine-2 receptor antibodies.[16] Many patients have MRI T2 hyperintense basal ganglia abnormalities and show signs of CSF inflammation including oligoclonal bands.[16] Immune therapy is the mainstay of treatment.[16] In the past, encephalitis with dominant involvement of the basal ganglia was given a variety of names, including encephalitis lethargica and (infantile) bilateral striatal necrosis.[16] These disorders and autoimmune basal ganglia encephalitis may all be part of the same clinical entity.[16]

Infections

DC caused by infection is relatively rare, but has been reported in children with viral infections, tuberculosis, mycoplasma or toxoplasmosis.[19] Infection by flaviviruses is an important cause of DC, the most common being Japanese encephalitis.[19] Other viruses associated with DC include influenza viruses, herpes viruses (including herpes simplex and herpes zoster) and measles viruses, which may lead to subacute sclerosing panencephalitis.[7,8] The main bacterial infections are tuberculosis and infection by Mycoplasma pneumoniae.[8] Infection should be suspected in any child with dystonia and pre-existing immunodeficiency or signs of meningoencephalitis or encephalitis. Detecting the infectious agent may be important for the type of therapy chosen and therefore serum and CSF investigations are indicated in addition to neuroimaging.

2.3.3.2 – Treatable IEM

IEM are highly heterogeneous. For most clinicians who do not work daily with IEM, it will be virtually impossible to recognise all these often extremely rare conditions. Fortunately, since all IEM can be detected with NGS diagnostics, early identification is only necessary for those IEM where timely treatment can improve the outcome.[20]

In general, an important clue for an IEM is a complex clinical picture comprising both neurological and non-neurological features. An overview of treatable IEM associated with DC is provided in supplementary **Table S3**. We defined 'treatable' as the availability of a therapy that might lead to the improvement or prevention of symptoms. We will highlight five significant subgroups of treatable IEM that may cause DC.

Organic acidurias

Organic acidurias can present both acutely and intermittently and are associated with 'intoxication-like' non-specific symptoms, such as vomiting and anorexia, progressing towards encephalopathy. Episodes are frequently triggered by intercurrent illness, dietary changes or prolonged fasting.[21]

When the underlying enzymatic defect is severe, onset will be in the newborn period. Milder phenotypes may present later as a slowly progressive disorder or with an intermittent course. Examples of organic acidurias associated with DC are propionic aciduria, methylmalonic aciduria, cobalamin defects and glutaric aciduria type I.[22]

GLUT-1 deficiency

GLUT-1 deficiency, caused by mutations in the SCL2A1 gene, can give rise to paroxysmal dystonia triggered by prolonged exercise.[23] This phenotype is also referred to as paroxysmal exertion-induced dystonia. The SCL2A1 gene encodes for the glucose transport protein 1, and mutations in this gene compromise glucose transport to the brain. Paroxysmal dystonia can be the sole feature, but developmental delay, spasticity, ataxia and epilepsy can also be part of the phenotype. A ketogenic diet is the current gold standard for treatment and has proven to be beneficial in most cases.[23]

Metal storage

Wilson's disease (WD) and dystonia with brain manganese accumulation (DBMA), caused by *SLC30A10* mutations, are both metal storage disorders in which symptoms can be fully or partly prevented by timely treatment.[24,25] In both disorders, a combination of neurological symptoms and hepatic involvement is usually present. Other manifestations are psychiatric symptoms and a corneal Kayser-Fleischer ring in WD and parkinsonism and polycythaemia in DBMA. Indicative biochemical findings include low serum copper and ceruloplasmin in WD and hypermanganesaemia in DBMA.

Lysosomal storage

Niemann-Pick type C is a clinically heterogeneous disorder in which the presenting phenotype depends on the age of onset. Infants can present with ascites and liver or pulmonary disease. The classic presentation in mid to late childhood consists of ataxia, a supranuclear vertical gaze palsy, psychiatric symptoms, dystonia and dementia, whereas the clinical picture in adults is dominated by psychiatric symptoms and cognitive decline.[26] Recently, treatment with miglustat has been shown to stabilise the progression of neurological symptoms, including in pediatric patients.[27]

Dopa-responsive dystonias

Dopa-responsive dystonias (DRDs) are a group of disorders with a more insidious onset, probably representing 5% of childhood dystonias.[28] The autosomal dominant form, GTP-cyclohydrolase deficiency, is most common. This form is also known as Segawa disease and shows an excellent and sustained response to low doses of levodopa.[29] Typically, there is a diurnal fluctuation of symptoms, and associated parkinsonism. Furthermore, two autosomal recessive forms of DRD have been identified: tyrosine hydroxylase deficiency and sepiapterin reductase deficiency, both often accompanied by intellectual disability and ophthalmological problems like oculogyric crisis, upward gaze and ptosis.[30]

Since DRD features can be non-specific and can show considerable phenotypic variability, DRDs are frequently misdiagnosed as CP.[30] This may result in a considerable delay in diagnosis and adequate treatment.[29,30]

In addition to biochemical and molecular studies, a levodopa trial can be used as a diagnostic procedure. However, it should be noted that a positive response on a levodopa trial is not specific for the classic DRDs, but can also be seen in other disorders such as ataxia telangiectasia and GLUT1-deficiency.[31,32]

2.3.3.3 – Classification of genetic dystonias

The genetic forms of dystonia including IEM, may be categorised into two groups. The first group consists of the monogenetic forms of dystonia with assigned genetic loci identified as *DYT1-25*, formerly named 'primary dystonias' and 'dystonia plus syndromes'. These disorders are characterised by isolated dystonia, or dystonia combined with parkinsonism or myoclonus.[1] The second group consists of genetic disorders in which dystonia is an important feature among several other neurological and systemic features. On axis I of the latest dystonia classification, these co-occurring neurological or systemic manifestations are classified as 'associated features'.[1] Important associated features in children include: ataxia, epilepsy, mental retardation, spasticity, hypotonia, abnormal eye movements, neuropathy, deafness, ophthalmological signs, hepatosplenomegaly, psychiatric and dysmorphic features. These features are decisive for accurate phenotyping and a prerequisite for correct interpretation of NGS results.

2.3.4 – NGS methodology

Genetic techniques using massive parallel sequencing are called NGS. With these new techniques, sequencing the entire genome of a patient (whole-genome sequencing; WGS), the coding regions (exons) of every gene (whole-exome sequencing; WES) or targeting specific disease-causing genes (targeted resequencing; TRS) have all become a reality in DNA diagnostics. Technical details of the specific methods fall outside the scope of this review, but are described elsewhere.[33]

It is important to recognize that with WGS or WES approaches, information for all genes will become available, including those not relevant to the diagnostic question. These genes need to be excluded to restrict the data analysis to a list of known genes that might explain the phenotype. If the phenotype is unique and no mutation is found in the selected genes, the information about the excluded genes may be used to hunt for new disease-causing genes. The drawbacks of WGS and WES are high costs, the risk of unsolicited findings, and coverage that is usually less than in TRS panels, compromising the diagnostic accuracy. In TRS panels, a preselected list of several known genes that cause dystonia are tested. By sequencing only preselected genes, the coverage significantly increases, contributing to diagnostic accuracy, and unsolicited findings are minimised, at significantly lower costs.

The important benefits of NGS diagnostics compared with regular biochemical procedures are that shipping DNA to referral centres is relatively cheap and straightforward, without stringent shipping conditions. In contrast, the costs and conditions of shipping samples, for instance, for (CSF) biochemical tests can be a serious hurdle in the present diagnostic process.

It is to be expected that in the near future the widespread use of NGS, both in research and in clinical diagnostics, will lead to many more reports of dystonia associated genes, and the list of associated genes will grow rapidly. However, it is important that independent confirmation of the causal relationship between gene variants and dystonia is performed, because in some of the recently annotated dystonia genes, variants in these genes also occur with high frequency in the general population.[34]

2.4 – A new diagnostic algorithm

Owing to the extraordinarily broad range of possible causes of DC, several algorithms have been developed to assist clinicians in making diagnostic decisions.[2,35,36] These algorithms are not widely applicable as they mainly focus on (rare) neurometabolic causes and do not make use of the availability of NGS methodologies. On the basis of our systematic literature review and our own clinical experience, we propose a new diagnostic algorithm with five steps (**Figure 1**).

2.4.1 – Step 1: Is it dystonia?

The first step in the algorithm is to record a careful history and perform a physical and neurological examination to determine that dystonia is an important feature.

Movement disorders that may be misdiagnosed as dystonia are listed in **Table 1**. In general, these 'pseudodystonias' have a known or presumed cause that is thought to differ from the causes of the broader dystonia group.[1] Applying the algorithm and using NGS testing is not advised in these conditions.

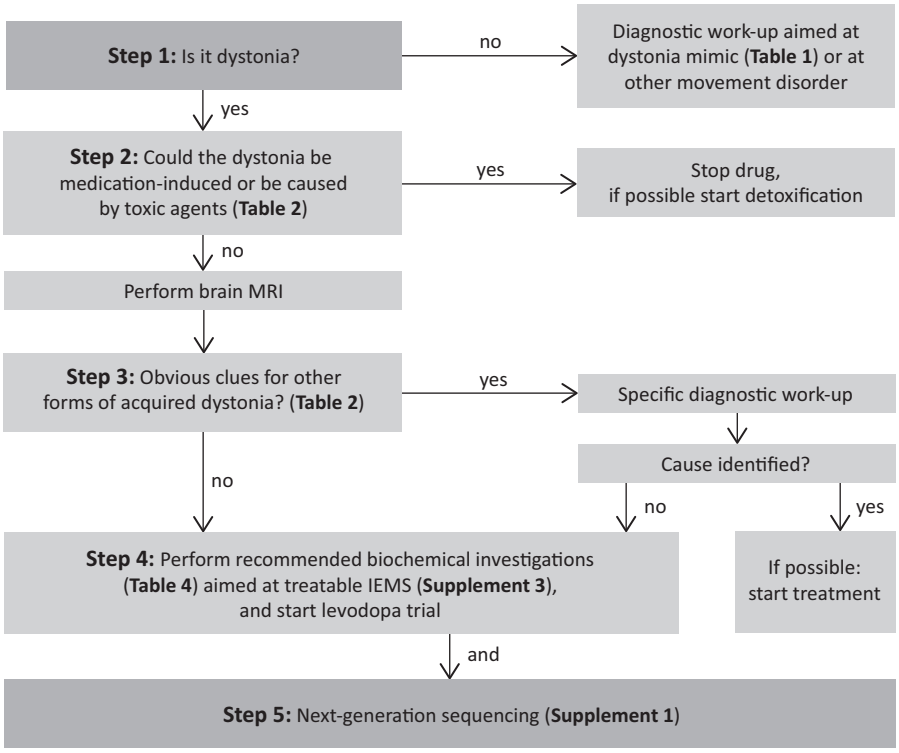
2.4.2 – Step 2: Could the dystonia be medication-induced or caused by toxic agents?

The second step is to verify exposure to any medication or toxic agents that could be causing the dystonia (**Table 2**). Treatment consists of discontinuing medication or prevention of further toxic exposure, and, if possible, detoxification.

2.4.3 – Step 3: Clinical clues suggesting acquired dystonia?

Step 3 is to consider whether the dystonia could be acquired. In **Table 3** we indicate red flags for acquired disorders with the main subgroups. These red flags are only defined to guide clinicians to a limited number of disorders in which immediate diagnosis and treatment is necessary to identify treatable disorders, preventing insults to the brain during the diagnostic process.

Figure 1 – Diagnostic algorithm of dystonia in children and adolescents



Abbreviation: IEM, inborn error of metabolism.

2.4.4 – Step 4: Biochemical investigations and levodopa trial

In any child with dystonia without obvious clues for an acquired cause, we recommend performing a laboratory workup (**Table 4**) aimed at identifying the treatable forms, before moving on to NGS testing. Of course this recommendation only applies for those centres where biochemical diagnostics will provide faster results than NGS testing, depending on the local facilities. CSF investigations are only recommended in selected patients (**Table 4**) because otherwise the diagnostic yield of CSF investigations is likely to be rather low.[37,38]

In addition to the laboratory investigations, we recommend that all patients receive a trial of levodopa with carbidopa.[30] The primary goal of the trial is diagnostic. However, an additional advantage is that levodopa can also give symptom relief in non-DRD dystonia.[39] The recommended starting dose of levodopa is 1 mg/kg/day, to be gradually increased until complete benefit or until dose-limiting side effects occur.[7] Most individuals respond to 4–5 mg/kg/day in divided doses.[40] Levodopa should be given for 3 months before considering the trial a failure.[39]

Table 4 – Biochemical investigations to identify treatable inborn errors of metabolism with dystonia as important feature

Laboratory test	In sample of	Disorder
Organic acids	Urine	glutaric aciduria type I, propionic aciduria, methylmalonic aciduria, cobalamin deficiencies
Lactate	Plasma	propionic aciduria, methylmalonic aciduria, biotin responsive basal ganglia disease
Pyruvate	Plasma	pyruvate dehydrogenase complex (PDC) deficiency
Acylcarnitines	Plasma	propionic aciduria, methylmalonic aciduria, glutaric aciduria type 1
Amino acids	Plasma	ornitine transcarbamylase deficiency, maple syrup urine disease, pterin defects
Homocysteine	Plasma	homocysteinuria
Copper, ceruloplasmin	Plasma, urine	Wilson's disease
Manganese	Plasma	dystonia with brain manganese accumulation
Biotinidase	Plasma	biotinidase deficiency
Creatine, guanidinoacetic acid	Plasma, urine	cerebral creatine deficiency syndrome 3 (AGAT deficiency), guanidinoacetate methyltransferase deficiency
Vitamin E (α-tocopherol)	Plasma	Ataxia with vitamin E deficiency (AVED)
Uric acid	Plasma	Lesch-Nyhan Syndrome
Cholestanol	Plasma	cerebrotendinous xanthomatosis
Glucose	CSF*, plasma	GLUT1 deficiency
Folate	CSF*	cerebral folate deficiency
HVA, 5-HIAA	CSF*	tyrosine hydroxylase deficiency
Pterines	CSF*, urine	GTP-cyclohydrolase 1 deficiency, 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency, aromatic l-amino acid decarboxylase (AADC) deficiency
Sepiapterin	CSF*	sepiapterin reductase deficiency

Note: performing this set of laboratory investigations is only recommended if obtaining the results of these tests will be faster than NGS testing.
** CSF: cerebrospinal fluid. Lumbar puncture seems justified only in selected cases with a high clinical suspicion for these disorders.*

2.4.5 – Step 5: NGS

Simultaneously with the biochemical investigations and the initiation of the levodopa trial, all possible genetic causes can be approached by using NGS diagnostic technologies. To facilitate this, we provide a list of DC associated genes (Supplementary **Table S1**). For those cases that remain unsolved after NGS testing, referral to a tertiary referral centre is recommended to further explore the possibilities to obtain an etiological diagnosis.

2.5 – Discussion

We provide a comprehensive overview of DC and propose a new diagnostic algorithm (**Figure 1**). This five-step approach provides guidance for clinicians to determine which patients may benefit from innovative genetic tests and those for whom other investigations are required first, while taking into account the importance of early recognition of acquired and treatable causes of DC.

Our proposed flowchart (**Figure 1**) differs from existing algorithms in that certain commonly used processing steps have been omitted, such as age at onset, temporal pattern (e.g., persistent or paroxysmal), associated features, and mode of inheritance.[2,35,36] Indeed, 'pattern recognition' based on these features has been important in the delineation of dystonia disorders and can still be successful in identifying classical phenotypes, especially by experts in the field.[1,8] However, these features were not included in our algorithm because many clinicians will have limited experience with these rare disorders and specific clinical patterns will easily remain unrecognised. In addition, recent insights from more widely applied NGS testing demonstrate that the clinical heterogeneity of many disorders is much larger than expected,[23,31] so clinical pattern recognition of milder, intermediate and unusual phenotypes remains problematic.

Nevertheless, careful clinical phenotyping still remains indispensable for two reasons. First, clinicians need to define, on the basis of these clinical parameters, the *a priori* risk that the patient is indeed suffering from a genetic disorder. NGS methodology should not be used when the *a priori* risk is low, because the numerous genes being tested increase the chance that variants will be misinterpreted as disease-causing, in genes that are unlikely to explain the clinical phenotype. Second, closely related to the first reason, detailed phenotyping is key when the results of NGS diagnostic strategies are available and need to be interpreted. As Hennekam and Biesecker[41] clearly stated, NGS and computers will not magically make patient diagnoses for us. Instead, there will be a shift from a pre-NGS-test differential diagnostic mode to a post-NGS-test diagnostic assessment mode.[41] Thus, the diagnostic skills of clinicians will be integrated into the evaluation of NGS test results, to make molecular diagnoses together with laboratory staff.

Notably, clinicians using NGS diagnostics should be aware that there are some technical pitfalls in the application of NGS diagnostics such as a limited ability to detect large structural rearrangements. In DC, this is particularly relevant if no causative mutation in a gene can be identified by NGS techniques, while at the same time the clinical picture is compatible with, for example, myoclonus dystonia or paroxysmal kinesigenic dyskinesia, both disorders that may be caused by deletions (in *SCGE* and *PRRT2,* respectively). In these cases, additional genetic tests detecting deletions are still required, such as multiplex ligation-dependent probe amplification or array comparative genomic hybridization (array-CGH).[42]

At present we live in a period of transition between emerging NGS diagnostic tests and changing costs, budgets and availability of diagnostic procedures. In the future, NGS tools will become

increasingly available in many areas of clinical diagnostics and clinical decision-making, and will be incorporated in our daily work and change our daily routines. Although not a panacea, the advantages of this new strategy will be earlier diagnosis, avoidance of unnecessary investigations, and the possibility of genetic counselling for family members. It will crucially shorten the time DC patients and their families spend in uncertainty awaiting a definitive diagnosis.

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Supplementary Table S1 – Overview of genes that may cause dystonia in children and adolescents

Gene (OMIM)	Disease name/phenotype	Mode of inheritance
1 – (Formerly called) Primary dystonias (DYTs):		
TOR1A (605204)	DYT1: Early-onset generalised primary torsion dystonia (PTD)	AD
TUBB4A (602662)	DYT4: Whispering dystonia	AD
GCH1 (600225)	DYT5: GTP-cyclohydrolase 1 deficiency	AD
THAP1 (609520)	DYT6: Adolescent onset torsion dystonia, mixed type	AD
PNKD/MR1 (609023)	DYT8: Paroxysmal nonkinesigenic dyskinesia	AD
SLC2A1 (138140)	DYT9/18: Paroxysmal choreoathetosis with episodic ataxia and spasticity/ GLUT1 deficiency syndrome-1	AD
PRRT2 (614386)	DYT10: Paroxysmal kinesigenic dyskinesia	AD
SGCE (604149)	DYT11: Myoclonus-dystonia	AD
ATP1A3 (182350)	DYT12: Rapid-onset dystonia parkinsonism	AD
PRKRA (603424)	DYT16: Young-onset dystonia parkinsonism	AR
ANO3 (610110)	DYT24: Primary focal dystonia	AD
GNAL (139312)	DYT25: Primary torsion dystonia	AD
2 – Inborn errors of metabolism:		
GCDH (608801)	Glutaric aciduria type 1	AR
PCCA (232000)	Propionic aciduria	AR
PCCB (232050)	Propionic aciduria	AR
MUT (609058)	Methylmalonic aciduria	AR
MMAA (607481)	Cobalamin A deficiency	AR
MMAB (607568)	Cobalamin B deficiency	AR
MMACHC (609831)	Cobalamin C deficiency	AR
C2orf25 (611935)	Cobalamin D deficiency	AR
MTRR (602568)	Cobalamin E deficiency	AR
LMBRD1 (612625)	Cobalamin F deficiency	AR
MTR (156570)	Cobalamin G deficiency	AR
CBS (613381)	Homocysteinuria	AR
PCBD (126090)	Hyperphelaninemia variant D	AR
TH (191290)	Tyrosine hydroxylase deficiency	AR
SPR (182125)	Sepiaterine reductase deficiency	AR

Supplementary Table S1 – *Continued*

Gene (OMIM)	Disease name/phenotype	Mode of inheritance
QDPR (612676)	Dihydropteridine reductase (DHPR) deficiency	AR
PTS (612719)	6-Pyruvoyltetra-hydropterin synthase (PTPS) deficiency	AR
DDC (107930)	Aromatic L-amino acid decarboxylase deficiency	AR
SLC19A3 (606152)	Thiamine transporter deficiency (formerly Biotin responsive basal ganglia disorder)	AR
GAMT (601240)	Guanidinoacetate methyltransferase deficiency	AR
GATM (602360)	Cerebral creatine deficiency syndrome 3 (AGAT deficiency)	AR
NPC1 (607623)	Niemann Pick type C	AR
NPC2 (601015)	Niemann Pick type C	AR
ATP7B (606882)	Wilson's disease	AR
SLC30A10 (611146)	Dystonia with brain manganese accumulation	AR
PDHA1 (300502)	Pyruvate dehydrogenase E1-alpha deficiency	XD
PDHX (608769)	Pyruvate dehydrogenase E3-binding protein deficiency	AR
PDHB (179060)	Pyruvate dehydrogenase E1-beta deficiency	AR
DLAT (608770)	Pyruvate dehydrogenase E2 deficiency	AR
PDP1 (605993)	Pyruvate dehydrogenase phosphatase deficiency	AR
LIAS (607031)	Pyruvate dehydrogenase lipoic acid synthetase deficiency	AR
BTD (609019)	Biotinidase deficiency	AR
GALT (606999)	Galactosemia	AR
ADCK3 (606980)	Coenzyme Q10 deficiency	AR
MTP (157147)	Abetalipoproteinemia (Bassen-Kornzweig syndrome)	AR
FOLR1 (136430)	Cerebral folate deficiency	AR
MOCS1 (603707)	Molybdenum cofactor (sulfite oxidase) deficiency type A	AR
OTC (300461)	Ornitine transcarbamylase deficiency	XR
HPRT2 (308000)	Lesch-Nyhan Syndrome	XR
ALDH5A1 (610045)	Succinic semialdehyde dehydrogenase deficiency	AR
SLC6A3 (126455)	Infantile parkinsonism-dystonia (Dopamine transporter deficiency)	AR
BCKDHA (608348)	Maple syrup urine disease type Ia	AR
BCKDHB (248611)	Maple syrup urine disease type Ib	AR
DBT (248610)	Maple syrup urine disease type II	AR

Supplementary Table S1 – *Continued*

Gene (OMIM)	Disease name/phenotype	Mode of inheritance
DLD (238331)	Dihydrolipoamide dehydrogenase deficiency (Maple syrup urine disease type III)	AR
ETHE1 (608451)	Ethylmalonic encephalopathy	AR
SLC6A8 (300036)	Cerebral creatinine deficiency syndrome 1	XR
SLC6A9 (608893)	Hartnup disorder	AR
SERAC1 (614725)	3-methylglutaconic aciduria with deafness, encephalopathy, and Leigh-like syndrome (MEGDEL)	AR
SUOX (606887)	Sulfocysteinuria	AR
FUCA1 (612280)	Fucosidosis	AR
GLB1 (611458)	GM1-gangliosidosis	AR
HEXA (606869)	Tay-Sachs disease (GM2-gangliosidosis type 1)	AR
HEXB (606873)	Sandhoff disease (GM2-gangliosidosis type 2)	AR
CLN3 (607042)	Neuronal ceroid lipofuscinosis 3 (Batten disease)	AR
TPP1 (607998)	Neuronal ceroid lipofuscinosis 2	AR
ARSA (6007574)	Metachromatic leukodystrophy (Arylsulfatase A deficiency)	AR
SLC16A2 (300095)	Allan-Herndon-Dudley syndrome (monocarboxylate transporter-8 (MCT8) deficiency)	XD
2.1 Mitochondrial disorders:		
POLG (174763)	Alpers/MNGIE/SANDO (Mitochondrial DNA depletion syndrome 4)	AR
SUCLA2 (603921)	Mitochondrial DNA depletion syndrome 5	AR
MPV17 (137960)	Mitochondrial DNA depletion syndrome 6 (hepatocerebral type)	AR
C2orf10 (606075)	Mitochondrial DNA depletion syndrome 7 (hepatocerebral type)	AR
NDUFS1 (157655)	Mitochondrial complex I deficiency	AR
NDUFS3 (603846)	Mitochondrial complex I deficiency	AR
NDUFS4 (602694)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFS7 (601825)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUSF8 (602141)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFA2 (602137)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFA9 (603834)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFA10 (603835)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFA12 (614530)	Mitochondrial complex I deficiency/Leigh syndrome	AR

Supplementary Table S1 – *Continued*

Gene (OMIM)	Disease name/phenotype	Mode of inheritance
NDUFAF2 (609653)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFAF5 (612360)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFAF6 (*C8orf38*) (612392)	Mitochondrial complex I deficiency/Leigh syndrome	AR
FOXRED1 (613622)	Mitochondrial complex I deficiency/Leigh syndrome	AR
NDUFV1 (161015)	Mitochondrial complex I deficiency/infantile bilateral striatal necrosis	AR
SDHA (600857)	Mitochondrial complex II deficiency (Succinate dehydrogenase deficiency)	AR
SDHAF1 (612848)	Mitochondrial complex II deficiency (Succinate dehydrogenase assembly factor 1 deficiency)	AR
BCS1L (603647)	Mitochondrial complex III deficiency/Leigh syndrome	AR
COX10 (602125)	Mitochondrial complex IV deficiency/Leigh syndrome	AR
COX15 (603646)	Mitochondrial complex IV deficiency/Leigh syndrome	AR
COX20 (614698)	Mitochondrial complex IV deficiency	AR
SURF1 (185620)	Mitochondrial complex IV deficiency/Leigh syndrome	AR
TACO1 (612958)	Mitochondrial complex IV deficiency/Leigh syndrome	AR
MTATP6 (516060)	Mitochondrial complex V deficiency/Leigh syndrome	Mitochondrial
MTND1 (516000)	Leber optic atrophy and dystonia	Mitochondrial
MTND3 (516002)	Leber optic atrophy and dystonia	Mitochondrial
MTND1 (516003)	Leber optic atrophy and dystonia	Mitochondrial
MTND1 (516006)	Leber optic atrophy and dystonia	Mitochondrial
MTATP6 (516060)	Mitochondrial infantile striatonigral degeneration	Mitochondrial
3 – Other disorders, including neurodegenerative diseases:		
PANK2 (606157)	Neurodegeneration with brain iron accumulation (NBIA) 1/HARP	AR
PLA2G6 (603604)	Neurodegeneration with brain iron accumulation (NBIA) 2/PARK14	AR
FTL (134790)	Neurodegeneration with brain iron accumulation (NBIA) 3	AD
C19orf12 (614297)	Neurodegeneration with brain iron accumulation (NBIA) 4	AR
Wdr45 (300894)	Neurodegeneration with brain iron accumulation (NBIA) 5	XD
CYP27A1 (606530)	Cerebrotendinous xanthomatosis	AR
PLP1 (300401)	Pelizaeus-Merzbacher disease	XR
MTP (157147)	Abetalipoproteinemia (Bassen-Kornzweig syndrome)	AR

Supplementary Table S1 – *Continued*

Gene (OMIM)	Disease name/phenotype	Mode of inheritance
FA2H (611026)	Spastic paraplegia type 35	AR
ATP13A2 (610513)	Kufor-Rakeb syndrome (PARK9)	AR
PRKN (602544)	Juvenile Parkinson disease type 2 (PARK2)	AR
PINK1 (608309)	Early onset Parkinson disease type 6 (PARK6)	AR
DJ1 (602533)	Early onset Parkinson disease type 7 (PARK7)	AR
FBXO7 (605648)	Early onset Parkinson disease type 15 (PARK15)	AR
SYNJ1 (604297)	Early-onset atypical parkinsonism (PARK20)	AR
SPG11 (610844)	Spastic paraplegia type 11	AR
AP4B1 (607245)	Spastic paraplegia type 47	AR
TREX1 (606609)	Aicardi-Goutieres syndrome 1	AR,AD
RNASEH2B (610362)	Aicardi-Goutieres syndrome 2	AR
RNASEH2C (610330)	Aicardi-Goutieres syndrome 3	AR
RNASEH2A (606034)	Aicardi-Goutieres syndrome 4	AR
SAMHD1 (606754)	Aicardi-Goutieres syndrome 5	AR
ADAR1 (146920)	Aicardi-Goutieres syndrome 6	AR,AD
NUP62 (605815)	Infantile striatonigral degeneration	AR
NKX2-1/TITF1 (600635)	Benign hereditary chorea	AD
ATM (607585)	Ataxia-Telangiectasia	AR
VPS13A (605978)	Choreoacanthocytosis	AR
COL4A1 (120130)	Porencephaly 1	AD
SEPSECS (613009)	Pontocerebellar hypoplasia type 2D	AR
CTC1 (613129)	Cerebroretinal microangiopathy with calcifications and cysts (CRMCC) (Coats plus syndrome)	AR
ALSIN (606352)	Juvenile amyotrophic lateral sclerosis 2	AR
TIMM8A (300356	Mohr-Tranebjaerg syndrome (Dystonia deafness syndrome	XR
BTK (300300)	X-linked agammaglobulinemia with hearing impairment, dystonia-parkinsonism, and progressive neurodegeneration	XR
BCAP31(300398)	Deafness, dystonia and central hypomyelination	XR

Supplementary Table S1 – *Continued*

Gene (OMIM)	Disease name/phenotype	Mode of inheritance
OPA3 (606580)	Optic atrophy with early onset pyramidal tract signs and dystonia	AR
ACTB (102630)	Juvenile onset dystonia	AD
ARFGEF2 (605371)	Periventricular nodular heterotopia and dystonia	AR
GRIK2 (138244)	Intellectual disability, behavioural disorder, epilepsy and dystonia	AR
HTT (613004)	Huntington disease	AD
C2orf37/DCAF17 (612515)	Woodhouse Sakati syndrome	AR
MECP2 (300005)	Rett syndrome	XD
FOXG1 (164874)	Rett syndrome, congenital variant	de novo
ARX (300382)	Partington syndrome/X-linked mental retardation	XR
ATN1 (607462)	Dentatorubral-pallidoluysian atrophy	AD
CACNA1B (601012)	Myoclonus-Dystonia-like syndrome with cardiac arrhythmias	AD

Abbreviations: AR: Autosomal recessive, AD: Autosomal dominant, XR: X-linked recessive, XD: X-linked dominant

Supplementary Box S2 – Search criteria systematic review

Search strategy:

We reviewed all papers regarding dystonia, both genetic and non-genetic, in three age groups (infancy, childhood and adolescence), which is from birth to 20 years of age.[1] The key terms we used were "dystonia" combined with (synonyms of) "children", "childhood", "adolescence" and "early onset", as well as (synonyms of) terms indicating possible etiologies including "genetic", "acquired", "primary", "secondary", "heredodegenerative", "hereditary", and "inborn errors of metabolism". All reviewed papers and abstracts were presented in English.

We considered using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool for selecting papers, developed by Whiting and colleagues (see Supplemental references). However, this tool proved not to be applicable as disorders causing dystonia of childhood are rare and the available evidence consisted only of small clinical trials, case series and expert opinion. For the same reason, not all items of the PRISMA Checklist (**Supplement 6**) are applicable.

Study selection:

Included literature and associated references involved at least one adequate description of: symptoms, signs, laboratory investigations (including metabolic evaluation), neuroimaging or genetic analysis, with supporting evidence for the etiological diagnosis. Included literature concerned at least two patients with the same condition, presenting with dystonia as an isolated, prominent or presenting symptom. Further references were retrieved manually from reference lists. Text books, Online Mendelian Inheritance in Man (OMIM) and GeneReviews were used for overviews of possible causes of dystonia. The list of genes (**Supplement 1**) is based on a detailed literature search up to October 20th 2014). The final reference list was generated on the basis of originality and relevance to the topic.

Key electronic search strategy for PubMed:

(dyston* AND (child* OR pediatric OR adolescent* OR (early onset) OR (early-onset))) AND (genetic OR primary OR hereditary OR heredodegenerative OR acquired OR secondary OR (inborn errors of metabolism))

Filters activated: Humans, English.

Supplementary Table S3 – Treatable inborn errors of metabolism with dystonia as important feature

IEM	Gene (OMIM)	Characteristic features besides dystonia	Treatment
Glutaric aciduria type 1	*GCDH* (608801)	Macrocephaly, developmental retardation, cardiomyopathy, encephalopathic crisis	Lysine restriction, carnitine supplementation, emergency treatment during intercurrent illness
Propionic aciduria	*PCCA* (232000) / *PCCB* (232050)	Developmental retardation, encephalopathic crisis, optic nerve atrophy, cardiomyopathy, alopecia, pancytopenia, (pseudo-) diabetes	Dietary protein restriction, carnitine supplementation emergency treatment during intercurrent illness
Methylmalonic aciduria	*MUT* (609058)	Developmental retardation, encephalopathic crisis, renal insufficiency, alopecia, pancytopenia, (pseudo-) diabetes	Dietary protein restriction, carnitine supplementation emergency treatment during intercurrent illness
Cobalamin A deficiency	*MMAA* (607481)	Developmental delay, recurrent vomiting, ataxia, spasticity, pancytopenia	Hydroxocobalamin, protein restriction
Cobalamin B deficiency	*MMAB* (607568)	Developmental delay, recurrent vomiting, ataxia, spasticity, hepatomegaly, pancytopenia	Hydroxocobalamin, protein restriction
Cobalamin C deficiency	*MMACHC* (609831)	SGA, microcephaly, failure to thrive, anemia, developmental delay, abnormal retinal pigmentation, seizures, psychiatric disease	Hydroxocobalamin
Cobalamin D deficiency	*C2orf25* (611935)	Developmental delay, intellectual disability, anemia, ataxia, nystagmus, behaviour problems	Hydroxo- / cyanocobalamin
Cobalamin E deficiency	*MTRR* (602568)	Developmental delay, intellectual disability, megaloblastic anemia, failure to thrive, ataxia, seizures, blindness	Hydroxo- / methylcobalamin, Betaine
Cobalamin F deficiency	*LMBRD1* (612625)	Developmental delay, intellectual disability, failure to thrive, frequent infections: stomatitis, ataxia, spasticity, pancytopenia	Hydroxocobalamin
Cobalamin G deficiency	*MTR* (156570)	Developmental delay, intellectual disability, megaloblastic anemia, failure to thrive, ataxia, seizures	Hydroxo- / methylcobalamin, Betaine

Supplementary Table S3 – *Continued*

IEM	Gene (OMIM)	Characteristic features besides dystonia	Treatment
Homocysteinuria	*CBS* (613381)	Mental retardation, behavioural disturbances, marfan-like appearance, myopia, ectopia lentis, osteoporosis, thromboembolic events	Methionine restriction, Betaine In some cases pyridoxine
GTPc1-deficiency (Segawa disease)	*GCH1* (600225)	Diurnal fluctuation, hypokinetic-rigid syndrome, psychiatric disorders	Levodopa-carbidopa (marked response)
Tyrosine hydroxylase deficiency	*TH* (191290)	Developmental delay, hypokinetic-rigid syndrome, diurnal fluctuation, oculogyric crises, autonomic disturbance	Levodopa
Sepiapterin reductase deficiency	*SPR* (182125)	Developmental delay, intellectual disability, diurnal variation, oculogyric crises, hypotonia, autonomic disturbance	Levodopa-carbidopa, 5-hydroxytryptophan
Dihydropteridine reductase (DHPR) deficiency	*QDPR* (612676)	Progressive developmental delay, seizures, microcephaly, parkinsonism	Levodopa-carbidopa, 5-hydroxytryptophan Tetrahydrobiopterin, Folinic acid, Phe-restricted diet
6-Pyruvoyltetra-hydropterin synthase (PTPS) deficiency	*PTS* (612719)	Developmental delay, seizures, microcephaly, parkinsonism, hypersalivation	Tetrahydrobiopterin, Levodopa/carbidopa, 5-hydroxytryptophan
Aromatic L-amino acid decarboxylase deficiency	*DDC* (107930)	Developmental delay, oculogyric crises, hypotonia, autonomic symptoms	Levodopa / dopamine agonists, pyridoxine, MAO inhibitors (therapy only effective in a minority of patients)
GLUT-1 deficiency	*SLC2A1* (138140)	Paroxysmal dyskinesias, epilepsy, psychomotor retardation, spasticity, ataxia, microcephaly	Ketogenic diet
Galactosemia	*GALT* (606999)	Failure to thrive, food intolerance, hepatomegaly, jaundice, cataract	Lactose restricted diet
Thiamine transporter deficiency (formerly Biotin responsive basal ganglia disorder)	*SLC19A3* (606152)	Subacute encephalopathy, dysarthria, and dysphagia, severe rigidity, quadriparesis	Thiamine and Biotin
Guanidinoacetate methyltransferase deficiency	*GAMT* (601240)	Intellectual disability, seizures, autistic behaviour, hypotonia	Creatine, Ornithine, dietary arginine restriction

Supplementary Table S3 – *Continued*

IEM	Gene (OMIM)	Characteristic features besides dystonia	Treatment
Cerebral creatine deficiency syndrome 3 (AGAT deficiency)	*GATM* (602360)	Mental retardation with severe delay of speech, myopathy causing muscle weakness, failure to thrive	Oral creatine supplementation
Niemann-Pick type C	*NPC1* (607623) / *NPC2* (601015)	Dementia, psychiatric symptoms, epilepsy, ataxia, supranuclear vertical gaze palsy, cholestatic icterus, liver failure	Miglustat
Wilson's disease	*ATP7B* (606882)	Chronic liver disease, Kayser-Fleischer rings, cardiomyopathy, hemolysis	Zinc, Tetrathiomolybdate
Dystonia with brain manganese accumulation	*SLC30A10* (611146)	Chronic liver disease, polycythemia, parkinsonism, hypermanganesaemia	Chelation with intravenous disodium calcium edentate, Ferro fumarate
Pyruvate dehydrogenase complex (PDC) deficiency *(Mostly X-linked)*	*PDHA1* (300502) *PDHX* (608769) *PDHB* (179060) *DLAT* (608770) *PDP1* (605993) *LIAS* (607031)	Mental retardation, hypotonia, hypertonia, seizures, microcephaly, ataxia	Thiamine, ketogenic diet, dichloroacetate (DCA)
Biotinidase deficiency	*BTD* (609019)	Developmental delay, seizures, hypotonia, ataxia, vision and hearing problems, cutaneous abnormalities	Biotin
Coenzyme Q10 deficiency	*ADCK3* (606980)	Ataxia, exercise intolerance, seizures	Coenzyme Q10
Cerebrotendinous xanthomatosis	*CYP27A1* (606530)	Diarrhea, cataract, tendon xanthomas, neuropsychiatric symptoms, spasticity	Chenodeoxycholic acid
Abetalipoproteinemia (Bassen-Kornzweig syndrome)	*MTP* (157147)	Fat malabsorbtion, retinitis pigmentosa, ataxia, acathocythosis	Vitamin E, fat reduced diet
Ataxia with Vitamin E Deficiency (AVED)	*TTPA* (600415)	Ataxia, areflexia, loss of proprioception, dysdiadochokinesiahead titubation, decreased visual acuity	Vitamin E (alpha-tocopherol)
Cerebral folate deficiency	*FOLR1* (136430)	Epileptic seizures, mental retardation,	Folinic acid
Molybdenum cofactor (sulfite oxidase) deficiency type A	*MOCS1* (603707)	Intractable neonatal seizures, developmental delay, feeding difficulties, lens dislocation	Cyclic PMP

Supplementary Table S3 – *Continued*

IEM	Gene (OMIM)	Characteristic features besides dystonia	Treatment
Ornitine transcarbamylase deficiency *(X-linked)*	*OTC* (300461)	Mental retardation, episodic lethargy and irritability, coma, ataxia	Protein restricted diet with arginine supplementation, sodium benzoate
Maple syrup urine disease (type I and II)	*BCKDHA* (608348) / *BCKDHB* (248611) / *DBT* (248610)	Neonatal encephalopathy, ataxia, intercurrent illness	Leucine restricted diet, in some patients thiamine supplementation

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